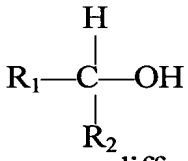
CLAIMS

I claim:

1. A method of minimizing toxicity of a retinoid having a carboxyl group, comprising the step of esterifying the carboxyl group with a highly sterically hindered alcohol.

2. The method of claim 1 wherein the sterically hindered alcohol comprises an alcohol selected from the group consisting of a secondary alcohol, a tertiary alcohol and mixtures thereof.

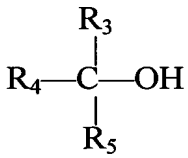
3. The method of claim 2 wherein the sterically hindered alcohol comprises a secondary alcohol having the formula



where R_1 and R_2 which may be the same or different, are each independently selected from the group consisting of a straight chain or branched alkyl group in all isomeric forms having 1 to 20 carbon atoms, and aryl.

4. The method of claim 3 wherein said alkyl group has 1 to 10 carbon atoms.

5. The method of claim 2 wherein the sterically hindered alcohol comprises a tertiary alcohol having the formula



where R_3, R_4 and R_5 which may be the same or different are each independently selected from the group consisting of a straight chain or branched alkyl group in all isomeric forms having 1 to 10 carbon atoms, and an aryl group.

6. The method of claim 5 wherein said alkyl group has 1 to 5 carbon atoms.

7. The method of claim 5 wherein the alcohol is t-butyl alcohol.

8. The method of claim 5 wherein the alcohol is pinacol.

9. The method of claim 5 wherein the alcohol is cholesterol.

10. The method of claim 1 wherein the retinoid is selected from the group consisting of

all-trans-retinoic acid;
9-cis-retinoic acid;
11-cis-retinoic acid;
13-cis-retinoic acid;
9,13-di-cis-retinoic acid;
TTNPB;
TTNN;
TTAB;
UAB8;
AM80;
AM580;
AM555S;
AGN 193836;
AGN 190299;
CD 2019;
CD 417;
R_o 48-2249;
R_o 44-4753;
R_o 10-9359;
SR 11254;
BMS 185354;
AGN 190299;
CD 437 (AHPN);
SR 11247;
SR 11217;
SR 11237;

AGN 191701;

LDG 100268;

LDG 100568;

LGD 100754;

R_o 25-7386;

BMS 188970;

SR 11004; and

SR 11203.

11. A method of reducing the toxicity of a retinoid which comprises:

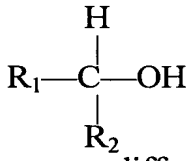
selecting a retinoid having a carboxyl group and having a desirable in vivo therapeutic activity;

selecting a highly sterically hindered alcohol which when reacted with the carboxyl group of the retinoid will provide an ester derivative that will modify the in vivo activity profile of said retinoid by reducing its in vivo toxicity; and

modifying the retinoid by derivatizing the carboxyl group with said highly sterically hindered alcohol to obtain said ester derivative.

12. The method of claim 11 wherein the sterically hindered alcohol comprises an alcohol selected from the group consisting of a secondary alcohol, a tertiary alcohol and mixtures thereof.

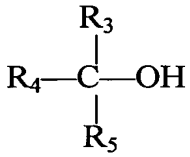
13. The method of claim 12 wherein the sterically hindered alcohol comprises a secondary alcohol having the formula



where R_1 and R_2 which may be the same or different, are each independently selected from the group consisting of a straight chain or branched alkyl group in all isomeric forms having 1 to 20 carbon atoms, and aryl.

14. The method of claim 13 wherein said alkyl group has 1 to 10 carbon atoms.

15. The method of claim 12 wherein the sterically hindered alcohol comprises a tertiary alcohol having the formula



where R_3, R_4 and R_5 which may be the same or different are each independently selected from the group consisting of a straight chain or branched alkyl group in all isomeric forms having 1 to 10 carbon atoms, and an aryl group.

16. The method of claim 15 wherein said alkyl group has one to five carbon atoms.

17. The method of claim 15 wherein the alcohol is t-butyl alcohol.

18. The method of claim 15 wherein the alcohol is pinacol.

19. The method of claim 15 wherein the alcohol is cholesterol.

20. The method of claim 11 wherein the retinoid is selected from the group consisting of

all-trans-retinoic acid;

9-cis-retinoic acid;

11-cis-retinoic acid;

13-cis-retinoic acid;

9,13-di-cis-retinoic acid;

TTNPB;

TTNN;

TTAB;

UAB8;

AM80;

AM580;

AM555S;

AGN 193836;

AGN 190299

CD 2019;

CD 417;

R_o 48-2249;

R_o 44-4753;

R_o 10-9359;

SR 11254;

BMS 185354;

AGN 190299;

CD 437 (AHPN);

SR 11247;

SR 11217;

SR 11237;

AGN 191701;

LDG 100268;

LDG 100568;

LGD 100754;

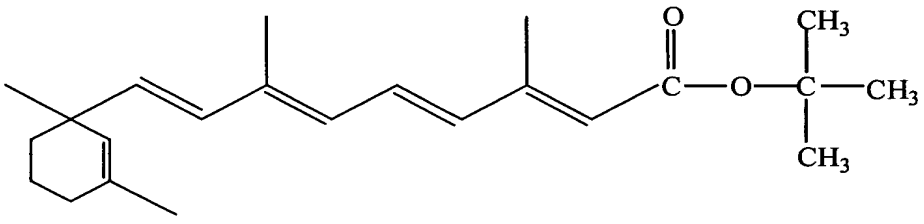
R_o 25-7386;

BMS 188970;

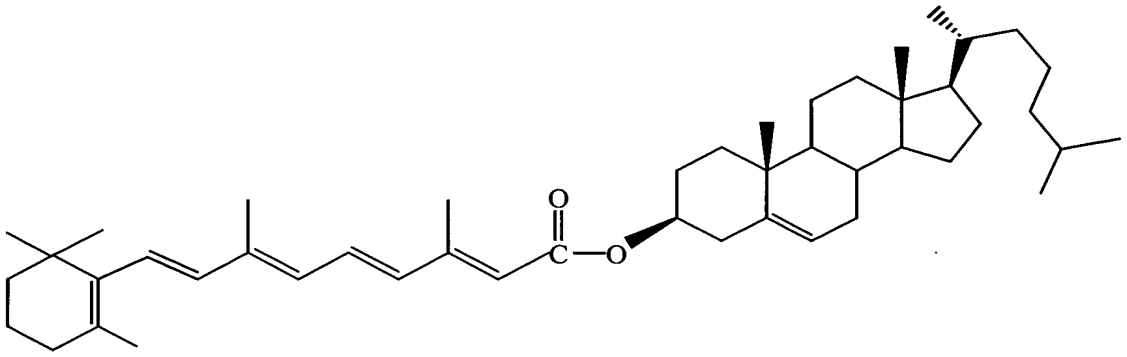
SR 11004; and

SR 11203.

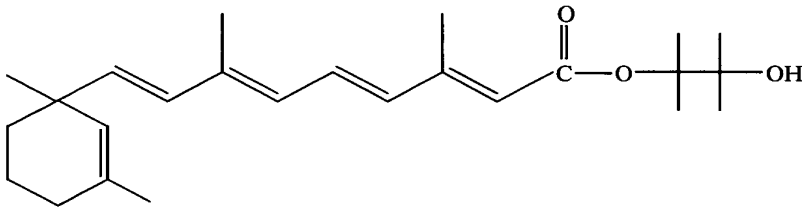
21. The method of claim 11 wherein said ester derivative has the formula:



22. The method of claim 11 wherein said ester derivative has the formula:



23. The method of claim 11 wherein said ester derivative has the formula:



24. A method of modulating the activity profile of a retinoid, comprising the steps of:

selecting a retinoid having a carboxyl group and having an in vivo therpeutic activity profile; and

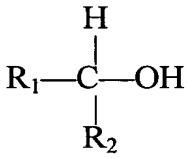
prolonging the activity profile of said retinoid by:

(a) selecting a highly sterically hindered alcohol which is hydrolyzable in vivo to the carboxyl group at a desired rate; and

(b) providing an esterified form of said retinoid by derivatizing the carboxyl group with said hindered alcohol.

25. The method of claim 24 wherein the sterically hindered alcohol comprises an alcohol selected from the group consisting of a secondary alcohol, a tertiary alcohol and mixtures thereof.

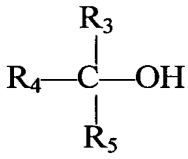
26. The method of claim 25 wherein the sterically hindered alcohol comprises a secondary alcohol having the formula



where R_1 and R_2 which may be the same or different, are each independently selected from the group consisting of a straight chain or branched alkyl group in all isomeric forms having 1 to 20 carbon atoms, and aryl.

27. The method of claim 26 wherein said alkyl group has 1 to 10 carbon atoms.

28. The method of claim 25 wherein the sterically hindered alcohol comprises a tertiary alcohol having the formula



where R_3, R_4 and R_5 which may be the same or different are each independently selected from the group consisting of a straight chain or branched alkyl group in all isomeric forms having 1 to 10 carbon atoms, and an aryl group.

29. The method of claim 28 wherein said alkyl group has 1 to 5 carbon atoms.

30. The method of claim 28 wherein the alcohol is t-butyl alcohol.

31. The method of claim 28 wherein the alcohol is pinacol.

32. The method of claim 28 wherein the alcohol is cholesterol.

33. The method of claim 24 wherein the retinoid is selected from the group consisting of

all-trans-retinoic acid;

9-cis-retinoic acid;
11-cis-retinoic acid;
13-cis-retinoic acid;
9,13-di-cis-retinoic acid;
TTNPB;
TTNN;
TTAB;
UAB8;
AM80;
AM580;
AM555S;
AGN 193836;
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R_o 48-2249;
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SR 11247;
SR 11217;
SR 11237;
AGN 191701;
LDG 100268;
LDG 100568;
LGD 100754;

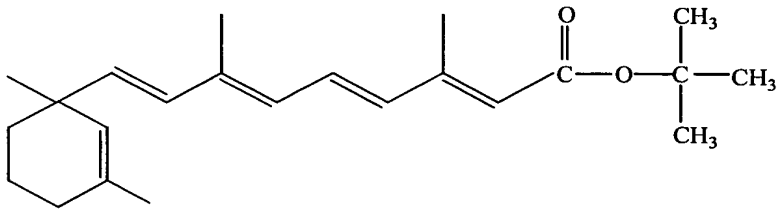
R_o 25-7386;

BMS 188970;

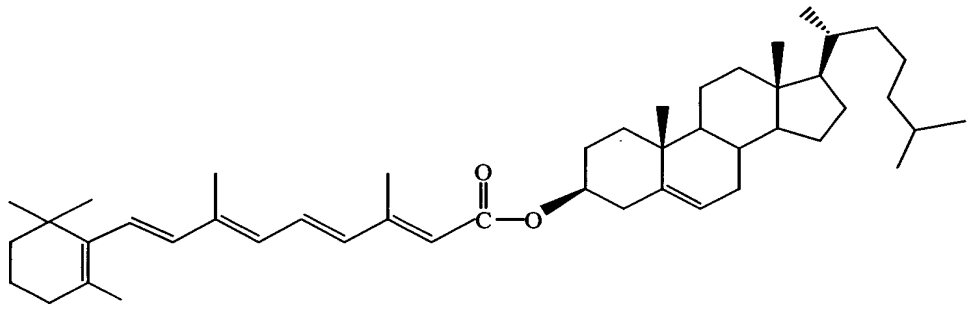
SR 11004; and

SR 11203.

34. The method of claim 24 wherein said ester derivative has the formula:



35. The method of claim 24 wherein said ester derivative has the formula:



36. The method of claim 24 wherein said ester derivative has the formula: